

# How to integrate biological research into society and exclude errors in biomedical publications?

Progress in theoretical and systems biology releases pressure on experimental research

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## Introduction

**T**his brief opinion proposes measures to increase efficiency and exclude errors in biomedical research under the existing dynamic situation. Rapid changes in biology began with the description of the three dimensional structure of DNA 60 years ago; today biology has progressed by interacting with computer science and nanoscience together with the introduction of robotic stations for the acquisition of large-scale arrays of data. These changes have had an increasing influence on the entire research and scientific community. Future advance demands short-term measures to ensure error-proof and efficient development. They can include the fast publishing of negative results, publishing detailed methodical papers and excluding a strict connection between career progression and publication activity, especially for younger researchers. Further development of theoretical and systems biology together with the use of multiple experimental methods for biological experiments could also be helpful in the context of years and decades. With regards to the links between science and society, it is reasonable to compare both these systems, to find and describe specific features for biology and to integrate it into the existing stream of social life and financial fluxes. It will increase the level of scientific research and have mutual positive effects for both biology and society. Several examples are given for further discussion.

Scientific information is neutral and unbiased since it reflects and describes the objective real world in a specific form using specialized concentrated language. Acquiring the reliable and valuable information requires nowadays more and more sophisticated equipment, resources and highly qualified researchers. However, the new knowledge is becoming emotionally attenuated upon interference with human society or specific human beings at definite periods of time.

Considering unidirectional time axis and changing human factor we get temporarily positive and negative results depending on the posed questions and expectations. The clear examples of well-established knowledge are laws of mechanics discovered by Sir Isaac Newton three centuries ago, laws of thermodynamics, Maxwell equations and quantum mechanics; they make the theoretical basement for modern technology being practically confirmed within centuries under certain physico-chemical limitations (range of speed, temperature, temporal and spatial resolution etc.). More recent new knowledge may not be neutral; for example, data about global warming due to increased economic activity of human civilization are rather negative since it requires essential recourses to overcome the fast consequences and potentially revert the processes. Results of short-term (usually one to three years) projects in biomedicine are often considered negative or positive especially for evaluation of specific chemicals to treat diseases (e.g., clinical trials).

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Scientific information is expressed in publications, databases and books; necessity of publishing results is important for sharing the new knowledge within the research community, reporting the results for funding bodies, getting funding to continue the research, for intellectual and professional development of researchers. Time scale with scheduled periods is important to integrate the science into the social and economic flux of the society. Time scale and high demand for robust and reliable initial results are vital for medical research.

Applicable to scientific research is a problem of optimal allocation of resources with maximum information outputs. It appears and has to be solved by a researcher or a group of researchers; the problem is changing with time and depends on many factors. An analog for methods to solve the problem is variational principle, which is widely used in science (especially in physics). Variational principle is applied to functional  $F$  depending on several variable functions and uses variational methods to find extremum of the functional. Assuming new knowledge being  $F$  (resources; funding; time; errors) would require to find the best functions achieving highest result with zero level of errors while aiming to minimal funding and time. The description sounds unnecessarily sophisticated; however, it is useful to set the upper level of abstraction and exclude emotional component. It's conceivable to introduce research efficiency depending on the real and ideal trajectories for obtaining the new knowledge. Assessing the value of the knowledge is the next step involving experts and taking longer time, so the parameter of research efficiency is not absolute; it is convenient for initial consideration.

The opinion paper compares biological and social systems describing the changes occurred in biomedical research within the past 60 years, and proposes short- and long-term measures to reduce errors and increase efficiency. The main part of the paper is aimed at applied biomedical research and prepared to stimulate further discussion.

### Existing and Changing Situation in Biomedicine

Within the past 60 years since the description of the three dimensional

structure of DNA by Watson and Crick<sup>1</sup> the landscape of biomedical sciences has drastically changed, however, not being completely supported by the corresponding changes in scientific traditions, lifestyle and, especially, in medical philosophy. Traditional reliable biochemistry and physiology with relatively simple methods are becoming complemented and often substituted by cell culture, gene sequencing, microarrays with robotic stations for data acquisition, computer modeling of single molecules and ensembles of molecules, online databases and publications. Adding the ideal requirement of absolute reproducibility and long-term checks for medical research worldwide, variable opportunities and situation in different countries, we get the existing developing situation. Similar situations and specific transformations for physics and chemistry centuries ago had been considered in more detail by philosopher of science Thomas Kuhn who proposed concept of scientific revolutions for shifting from one scientific paradigm and state of science-world-society to another one.<sup>2</sup> The sort of digital (computer) and molecular (switch to the level of single molecules) revolution is occurring in biomedicine and has significant influence on research and verification of biological theories and paradigms.

A complex way of introducing, changing and educating the human factor under the conditions depends on many parameters; it is reasonable to mention that, for example, computers were widely introduced to research only about 20 years ago, they accelerated data processing by many orders of magnitude. In parallel, large scale methods of data acquisition with robots emerged, they enormously increased the volume of information from an experiment and influenced the ways of thinking. The huge informational explosion is seen in the number of biomedical publications, it rose about 10 times since 1951 to about one million publications per year, over 90% of articles are in English nowadays (*vs* 50% in 1951).<sup>3</sup> Some areas are developing faster: the number of publications related to cell cycle-regulating protein p53 (data from PubMed <http://www.ncbi.nlm.nih.gov/pubmed/advanced>) increased over 100 times since the beginning of the 1980s reaching saturation by the next millennium.

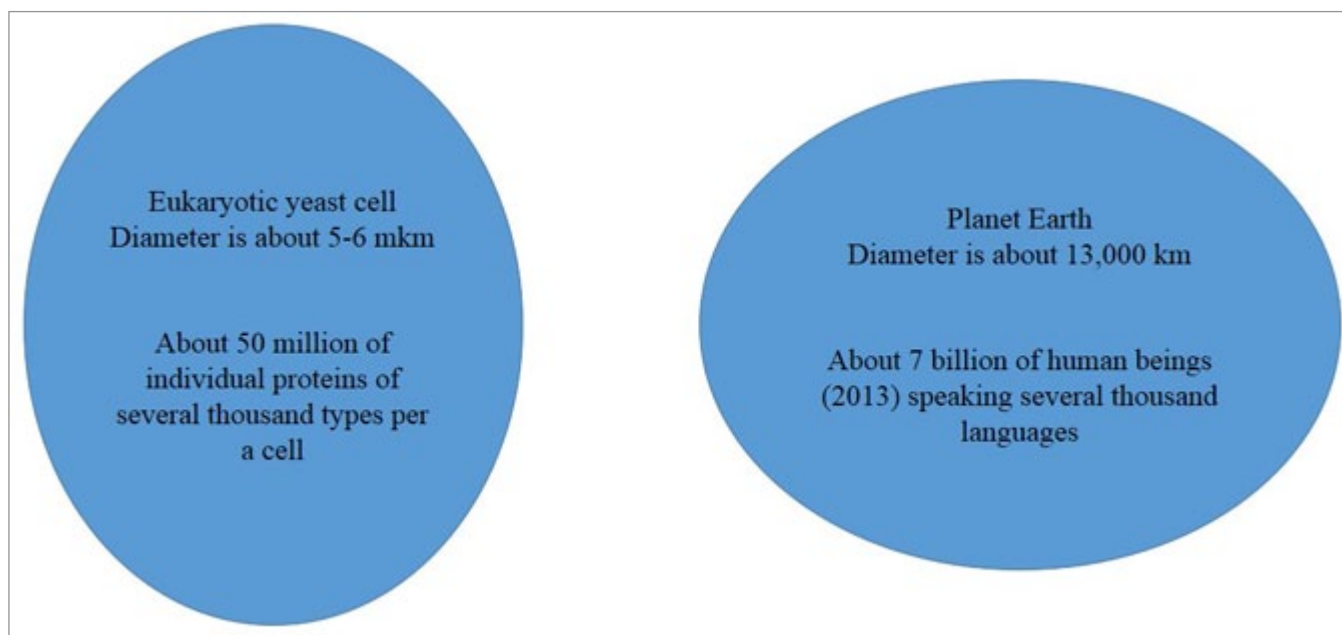
The aforementioned fast changes of rapidly developing branches of biology, especially related to practically important and well-funded biomedical aspects, may bring a load of experimental errors due to high demand for fast results, high pressure and changing human factor (which expresses at small time scales and due to increasing speed of research). Time and reproducibility will clarify the stream of results, while sometimes a good point *better not to do* at the moment could be used to save biological material, time and financial resources. Since the changes are not always gradual and consistent in science/methods/technology from one side and research community/society/medicine from the other side, the mismatches (or failed gaps under extreme situations) have to be filled with fast available (sometimes improper) solutions or even medical errors. Under a better outcome, the mismatches may result in extra resources and funding wasted.

A disputable example includes pesticide DDT, which was awarded Nobel Prize in Medicine in 1948<sup>4</sup> since it helped to fight typhus during the Second World War, but later proved to have some toxicity for humans (increasing cancer and neurological diseases and reducing reproductive health) and was banned in 1970s (e.g., reviewed in<sup>5</sup>).

Increasing competition leads to financial losses. It is worth mentioning high inconsistency of results between first microarrays for analysis of altered gene expression. Three similar microarrays from different companies showed overlap just in 4 genes from 24 to 93 detected.<sup>6</sup> It was proposed later that the start from the beginning could be the best way to continue with the technology.<sup>7</sup>

Recent rise in nanoscience promises big discoveries, however, needs a more thoughtful approach and a consideration of multiple explanations and experimental design. For example, nanoparticles simply interact with proteins under biological environment<sup>8</sup>; hence biological environment of organisms with proteins should be carefully considered in nanoscience research.<sup>9</sup>

Some areas are more prone to errors. For example, recent indications for sampled 53 publications in cancer research show that up to 90% of them may be incorrect.<sup>10</sup> The most serious problem is that over 60% of



**Figure 1.** Simplified comparison of a cloud of proteins in a eukaryotic yeast cell with human population demonstrates the comparative complexity of the two systems.

retracted papers in biomedical sciences are due to fraud or suspected fraud including plagiarism and duplicate publication, twice more than due to error.<sup>11, 12</sup> Moreover, percentage of retraction gradually rose 10 times since 1975 with the average time before retraction being about 3 years.<sup>12</sup> The rise appears to reflect the changes in behavior of authors and institutions over the time.<sup>13</sup> It poses serious questions about scientific ethics, research community and funding in the direction. The indications coincide with the drop in efficiency of research and development in the pharmaceutical industry, where expenses rose about 80 times for a new medical drug since 1950.<sup>14</sup> This might be a reason why money and production move out of developed European countries to new growing economies with a cheaper though less regulated and less qualified labor force.

### Biological Research and Society

It seems reasonable to compare biological and social systems trying to find specific features and peculiarities. Nowadays society seems more organized and complex than simple biological systems. A comparison of 1) Earth with human population consisting of seven billion human beings in 2013 (about 2.5 times more than in 1953)<sup>15</sup>

and speaking several thousand languages in about 200 countries with, for example, 2) a usual eukaryotic yeast cell containing only about 50 million of individual proteins of several thousand types<sup>16</sup> in less than ten compartments demonstrates the extent of complexity of the systems (Fig. 1). However, the presumed attractive coefficients (or attractive properties) of the systems could be different from the complexity.

Attractive coefficient of a system for a definite researcher could be introduced from the point of emotionally attenuated information enclosed in the system. The sort of advanced theory would vary between discrete and continuous systems; the theory doesn't seem to have been developed yet. Presumably it would require mathematics and basics of decision-making from neuroscience.<sup>17, 18</sup> A few obvious simple linear equations could be written for a discrete system with  $n = N$  elements:

$$K = N^2 - N, \quad (1)$$

where  $k = K$  is the number of connections  $k$  between  $n = N$  elements, then

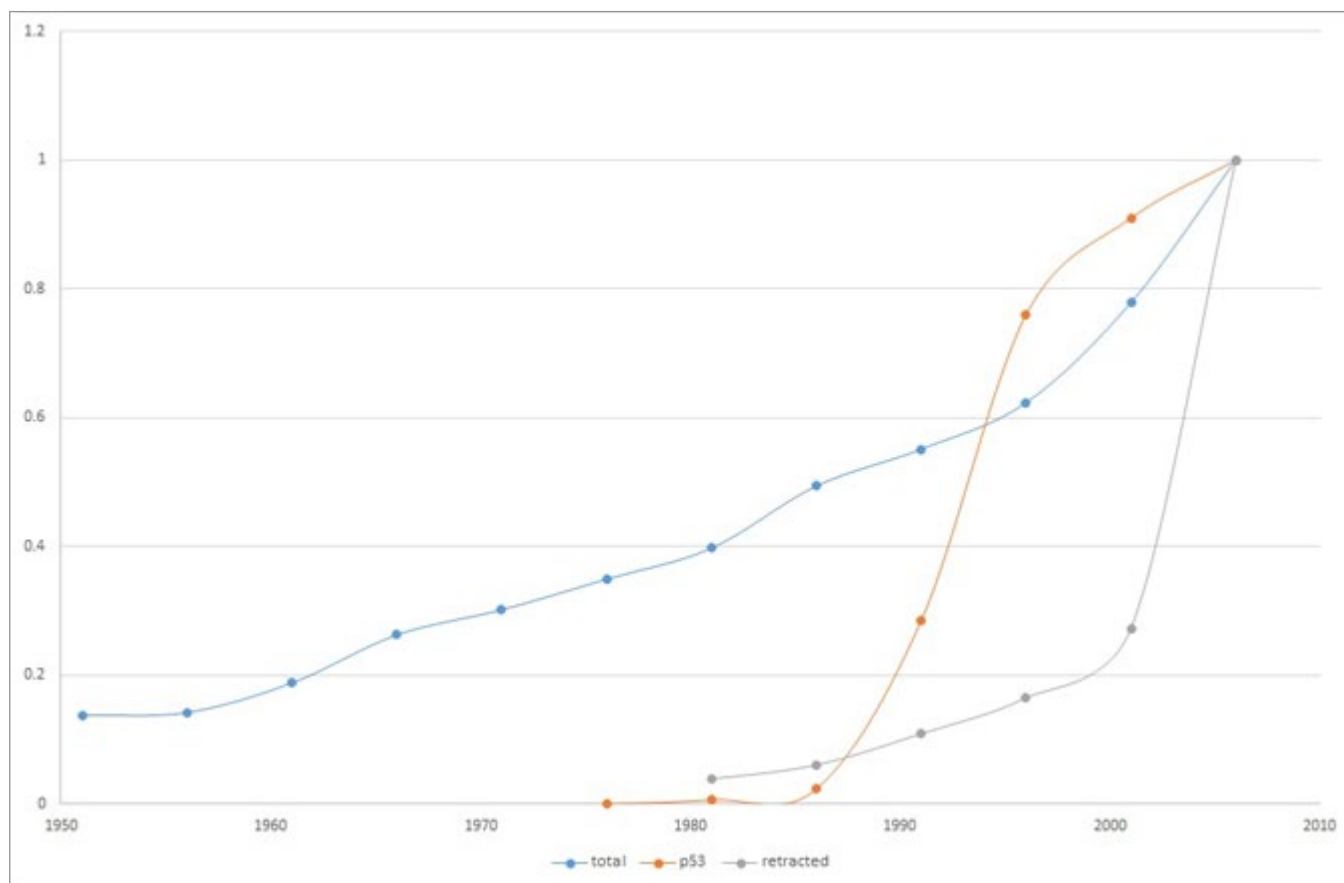
$$R = \sum_{i=1}^N (\alpha_i * n_i) + \sum_{j=1}^K (\beta_j * k_j), \quad (2)$$

where  $R$  is the total attractive coefficient, while  $\alpha$  and  $\beta$  are specific coefficients demonstrating informational value

of the corresponding element or connection between elements, respectively.

Pondering ideal researcher (without physiological demands and financial interest), it's conceivable to introduce minimal requirements expressed in certain specific coefficients  $\alpha$  and  $\beta$  (demand for unique equipment, high expectation time to get parameters, necessity of multiple efforts from groups of researchers, novelty and uniqueness of results, high social or biomedical demand for results etc.) for a relatively simple biological system to supersede the attractiveness of surrounding social system. Increase in number of elements starting from a eukaryotic yeast cell to one milliliter of yeast cell suspension with tens million of cells or considering multicellular organisms with trillions ( $10^{12}$ ) of cells of different types leads to a more common situation for a biomedical research.

Moreover, modern society is essentially based on known technology with nearly absolute and predictable (when compared with biology) established laws of physics and chemistry while the social life is tightly regulated by law and traditions; so different ways of thinking and better explanations with fewer promises for society are needed for biology. Applying simple digital logic and hard laws of economics to biology and further to



**Figure 2.** Increase in number of publications correlates with the faster increase of retracted publications. Data are normalized to the maximum of the corresponding curve (corresponding data point in 2006–2010) and taken with 5 year intervals. Data for total number of publications and publications for p53 protein are from PubMed; data for retracted publications are from the supplementary table.<sup>13</sup> Assuming average retraction time being 3 years for incorrect publications, it's clear that faster growing areas may have higher load of incorrect publication and need extra measures from authors and publishers.<sup>19</sup>

medicine, when estimating the conditions of norm and pathology or assessing the results, is not correct. It would seem that essential part of biomedical research is not sufficiently scheduled and predictable for being planned, realized and ever funded. However, biological objects and medical problems, not the society, determine the mainstream and intrinsic logic of research (Fig. 1.)

### Proposed Short-Term Measures

The new complex of biomedical science-research community-society nowadays compared with situation 60 years ago needs a series of novel measures to exclude errors and balance the further development. It requires short-term measures at the timescale of years and efforts of the whole scientific society for the timescale of decades. Research culture and values, ethics of researchers are slightly modifying

according to the dynamic changes of scientific environment.

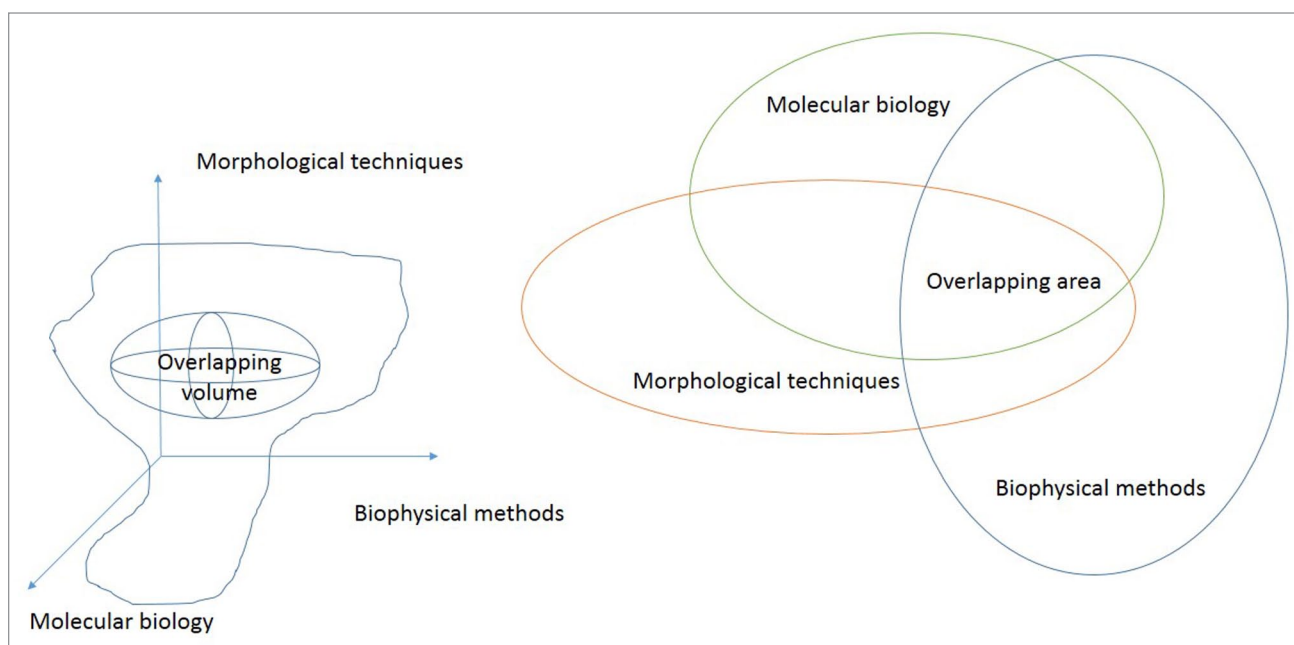
Several obvious simple measures starting from the level of publications could make the research more efficient and pondered. They could be as follows: 1) include fast publishing of negative results and 2) publish detailed and descriptive methods (a good example is Journal of Visualized Experiments <http://www.jove.com/>, which can essentially help with the reproducibility of the results though may restrict the creative potential of researchers), 3) exclude strong correlation between career progression and publication activity (especially for younger scientists in biomedical research), 4) provide more opportunities to express opinion and share results for students. It costs more to the whole community when fast incorrect, but highly desired results are spreading further (Fig. 2). The list is not comprehensive and points to reducing or neutralising

unavoidable emotional component arising from human factor and novelty of research.

From the other point, it might be reasonable to reclassify a large part of biomedical research, (not related to medicine) to animal and cell science research and shortcut recourses and experience from practical medicine with the rest of the field.

### Proposed Long-Term Measures

An additional factor to increase research efficiency is to make it “smarter,” more pondered. An important feature of the modern biomedical research is the increasing role of theoretical and systems biology. Recent development of systems biology attracted large numbers of mathematicians to biology, raising the level of quantitative understanding in experiments and mathematical culture of biologists.



**Figure 3.** Simple scheme of using several experimental dimensions (also depicted by overlapping circles) for achieving reliable results with multiple experimental lines of evidence.

Briefly, systems biology could be considered in a number of ways: 1) philosophy and way of integrative thinking for biological systems, 2) methodology for processing huge arrays of experimental data and dealing with exploding new information and 3) predictive models for experiments and biological objects. Obviously, new unexpected knowledge exists and complex biological systems may have multiple unpredictable responses and networks of reactions to the same stimulus, so systems biology is a powerful tool to help for experimental research, not a substitution of experiments.

The initial sparkling promises of systems biology had not been realized so far, however, the development continues and also provides educational and recourse-saving influence. Balanced experimental and theoretical biology will result in healthy

and effective biological research. A shift to theoretical aspects of biology is an additional way to stabilize the emerging rapid flow of scientific biomedical research.

An approach of using several different experimental methods for biological experiments (building experimental dimensions) aimed at solving a biological problem is another good way to increase research efficiency (Fig. 3). The proof of concepts based on overlapping results obtained using several methods provides higher reliability.

#### Author Contributions

V.V. conceived the arguments and wrote the paper.

#### Competing Interests

No competing interest declared. The views expressed in this paper should not be

attributed to any organization with which I am associated with. The short opinion expresses personal views and experience based on experimental work on several distinct projects in a few European and Asian countries over the past 20 years and, hence, may be biased or not comprehensive.

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